DEBATE

Aspirin dilemma
Remodelling the hypothesis from a fertility perspective

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Many clinical trials in obstetrics have failed to demonstrate improved outcomes with low-dose aspirin. This is not entirely surprising as prescribing aspirin for compromised tissue perfusion without insight into underlying pathology inevitably leads to suboptimal outcomes. We argue that a mismatch between the aspirin dose and the underlying pathology of altered tissue perfusion is the key factor to this failure. Based on this groundwork, we address the question of how best to optimize the dose of aspirin for use in fertility management, by providing examples from the assisted conception and recurrent miscarriage settings.

Key words: aspirin/fertility/IVF/miscarriages/prostaglandins

Introduction

New therapeutic applications for aspirin, a century-old drug, have been on the agenda for the last decade. Since the discovery of its mode of action, the classical analgesic, anti-inflammatory and antipyretic uses of aspirin have evolved into vascular and anti-platelet effects.

These new applications are of major interest in cardiology, because the platelet-rich, intravascular thrombus is central to the pathogenesis of diminished coronary perfusion. The value of low-dose aspirin in patients with established coronary artery disease has been recognized beyond doubt (Elwood and Stillings, 2000) and now it has been widely used for secondary prevention (European Action on Secondary Prevention by Intervention to Reduce Events, 2001).

Against this background, the limited success of aspirin use in obstetric practice has mystified many clinicians. Results of large trials on secondary prevention of pre-eclampsia have shown that if there is an indication for aspirin it is only in patients at a very high risk of developing severe, early-onset disease (Dekker and Sibai, 2001).

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Anti-prostaglandin effect

The benefit of aspirin is thought to derive from the inhibition of platelet thromboxane-A2 (TXA2) production (Reilly and FitzGerald, 1988). Because it is a potent platelet aggregator and vasoconstrictor, the effect is anti-thrombosis (Hamberg and Samuelsson, 1974). This is thought to offset the thrombophilic tendency, which leads to decreased tissue perfusion through platelet activation and arterial occlusion (Schror, 1997).

However, aspirin also inhibits the cyclo-oxygenase enzyme in the vascular endothelium, which is the source of prostacyclin, a potent inhibitor of platelet aggregation and a vasodilator (Moncada et al., 1976). The effect is then thrombogenic. Nevertheless, selective inhibition of platelets, which spares functional capacity of endothelium, is possible. This can alter the prostacyclin/thromboxane ratio favourably and results in increased tissue perfusion. As the effect occurs through the alteration of vascular tone, it is independent from the state of platelet activation.

The vascular and anti-platelet effects of aspirin are more or less simultaneous, but maximizing one will inevitably compromise the other. This is because no single dose of aspirin has been found to be completely selective for the inhibition of platelet TXA2 synthesis (FitzGerald et al., 1983; Lorenz et al., 1989; Madan and Sainani, 1995). Higher doses achieve more complete and rapid platelet inhibition and lower doses spare more endothelial cyclo-oxygenase activity.

Therefore, the optimal dose influencing vascular haemostatic regulation depends on the balance between anti-platelet and vascular tone, higher doses of aspirin are detrimental and lower doses should be used to achieve vasodilatation.
vasodilatory effects, and dose selection should be based on the reasons of impaired perfusion. In clinical practice, experience gained from obstetrics and cardiology can be applicable to IVF and recurrent miscarriage treatment.

IVF treatment and tissue perfusion

The evidence suggests that tissue perfusion is causally associated with the fertility potential of women (Goswamy et al., 1988). This provides a prognostically important factor in the outcome of assisted reproductive techniques. It has been suggested that in IVF cycles endometrial receptivity is related to uterine blood flow (Steer et al., 1992, 1995; Battaglia et al., 1997), and measures to improve tissue perfusion are associated with improved pregnancy rates (Wada et al., 1994; Rubinstein et al., 1999). This was shown both in an unselected IVF population (Rubinstein et al., 1999) and also in those with impaired uterine perfusion, who comprise up to 50% of all women undergoing IVF treatment (Goswamy et al., 1988; Wada et al., 1994). In this scenario, the best therapeutic approach depends on whether impaired tissue perfusion is associated with thrombophilic tendency or with high vascular tone.

As much as 53% of an unselected IVF population can be anti-phospholipid antibody (APA) positive (Check et al., 1998). In addition, women who failed to conceive after IVF treatment are more likely to have APA than those who conceived (Birkenfeld et al., 1994; Balasch et al., 1996). The relevance of this increased prevalence of APA has been scrutinized because of its association with thromboembolic events and possible implantation failure (Cowchock, 1991; Rai et al., 1996). Past studies revealed conflicting outcomes and strong differences of opinion emerged among researchers. While some reported no link between APA positivity and implantation outcome (Gleicher et al., 1994; Birdsall et al., 1996; Denis et al., 1997; Kowalik et al., 1997; Kutteh et al., 1997; Chilcott et al., 2000), others showed a negative role for APA in fertility and implantation (El-Roey et al., 1987; Birkenfeld et al., 1994; Geva et al., 1994; Sher et al., 1994; Dmowski et al., 1995). The most recent meta-analysis, however, found no significant association between APA and either clinical pregnancy or live birth rates (Hornstein et al., 2000).

In spite of the discrepancy between observational and interventional studies and critics over this meta-analysis (American Society for Reproductive Immunology Antiphospholipid Antibody Committee, 2000; Hornstein, 2000; Hornstein et al., 2000; Sher, 2000), the mere presence of these antibodies does not appear to affect IVF outcome, and there is no evidence that women undergoing IVF who are APA-positive are in a pro-thrombotic state.

Therefore, measures to improve tissue perfusion should focus on a prostacyclin-sparing low-dose range rather than the anti-platelet effect of high-dose protocols designed to combat the thrombophilic state.

Recurrent miscarriages and tissue perfusion

Fifteen percent of women with a history of recurrent miscarriage have persistently positive results for APA (Rai et al., 1997). An exaggerated haemostatic response leading to thrombosis of the uteroplacental vasculature has been suggested as the underlying pathology. In such women, pregnancy outcome appears to improve with aspirin alone (Rai et al., 1997). An even greater improvement was identified with the concomitant use of heparin (Kutteh, 1996; Rai et al., 1997). However, if there is no thrombophilic tendency, aspirin is not useful in the prevention of recurrent early pregnancy loss (Rai et al., 2000).

Therefore, a therapeutic approach should address tissue perfusion impaired by intravascular pathology. Aiming for a higher PGI2/TXA2 ratio with low dose aspirin is a suboptimal compromise as it does not improve tissue perfusion or pregnancy outcome as much as high doses can achieve (Blumenfeld et al., 1991; Tulppala et al., 1997).

In-depth discussion of APA and proposed mechanisms of action on dividing trophoblasts are kept beyond the scope of our argument and detailed information can be found elsewhere (McIntyre et al., 1993; Rai et al., 2000).

Conclusion

When we integrate the research findings and conceptual inferences, we can postulate that clinical benefit of aspirin critically depends on the dosage and timing of the regimen in relation to the underlying pathology of impaired tissue perfusion. The following propositions for clinical practice are drawn up on this assumption.

The presence of APA with or without antiphospholipid antibody syndrome (APS) does not appear to affect the establishment of pregnancy. Therefore, early attempts to improve uterine perfusion are not required in such women whose fertility is not impaired at the implantation stage. However, anti-thrombotic activity becomes crucially important in the placental development stage once implantation is complete. In such cases with APS, higher doses of aspirin can achieve improved outcomes that are further improved with the concomitant use of heparin. This indicates the need for a higher anti-thrombotic effect. Therefore, the dose of aspirin should be adjusted for maximum anti-thrombotic effect, even if it means lower prostacyclin concentrations. This requires doses much higher than the conventionally recognized low dose of 75 mg per day. Treatment should be started before 8 weeks gestation, but not necessarily before conception, in order to establish an adequate anti-platelet effect in the developing intervillous compartment.

In cases where fertility is impaired at the implantation stage, as in the IVF population, improvement of tissue perfusion is important at the earliest stages of implantation. In this setting, where the perfusion is impaired by vascular rather than intravascular pathologies, lower doses of aspirin, (≤75 mg daily) are required to achieve a better PGI2/TXA2 ratio and lower vascular tone. For maximum benefit, treatment should be started before conception.

References


